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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 09/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/397,967	IHLE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,36,38,42,43,45-48 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,38,42,43,45-48 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 2/26/02 in Paper No. 11 has been entered.

Claims 35, 36, 38, 42, 43, 45-48 and renumbered claim 51 are pending in the present application and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

The following modified rejection is necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 112

Claims 35, 36, 38, 43, 45-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) An isolated DNA molecule comprising a DNA sequence encoding the JAK3 kinase amino acid sequence of SEQ ID NO:16, wherein said JAK3 kinase has JAK kinase activity and undergoes tyrosine phosphorylation by at least one cytokine selected from the recited group; the same DNA molecule wherein said JAK3 kinase amino acid sequence of SEQ ID NO:16 have at least one conservative amino acid substitution; an expression vector comprising the same isolated DNA molecule and an isolated host cell comprising the same expression vector;

(b) An isolated DNA molecule comprising a DNA sequence encoding JAK3 kinase of SEQ ID NO:16, wherein said JAK3 kinase contains a peptide that binds a receptor for a cytokine selected from the recited group;

does not reasonably provide enablement for other embodiments in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to an isolated DNA molecule comprising a DNA sequence encoding at least 400 amino acids of a JAK3 kinase peptide of sequence SEQ ID NO:16, wherein said peptide has JAK kinase activity and undergoes tyrosine phosphorylation by at least one cytokine selected from the group consisting of IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, OSM, LIF, G-CSF, EPO, IFN-γ and GM-CSF or wherein said peptide binds a receptor for a cytokine selected from the aforementioned group; the same isolated DNA molecule wherein said molecule encodes a polypeptide having at least one conservative amino acid substitution or the same isolated DNA molecule comprising a 1500 base nucleotide DNA sequence encoding an amino acid sequence of SEQ ID NO:16; an expression vector and an isolated host cell comprising the same. Claim 43 is directed to an isolated DNA molecule comprising a DNA sequence encoding a JAK kinase peptide, said peptide having cytokine receptor binding domain. Claim 48 is directed to the same isolated DNA molecule of claim 43, wherein said molecule encodes a JAK3 kinase polypeptide that is at least 80-99% homologous to the amino acid sequence of SEQ ID NO:16, wherein the percent homology is determined by comparing sequence information using a GAP program having the recited default parameters.

The specification discloses the cloning of full-length cDNAs encoding for mouse JAK1, JAK2 and JAK3 kinases. The specification further demonstrates that JAK2 kinase is capable of associating with erythropoietin receptor or growth hormone receptor and it is phosphorylated and activated in response to erythropoietin, growth hormones, IL-3 and interferon-γ. The specification also teaches that JAK3 kinase is tyrosine phosphorylated and activated in response to IL-2 to IL-5, IL-7, IL-9, IL-11, G-CSF and GM-CSF in selected cells. Ciliary neurotrophic factor and related factors have also been shown to induce tyrosine phosphorylation of JAK1, JAK2 and Tyk2 in EW1 cells, and that these JAK kinases are probably associated with the membrane proximal region of the CNTF β receptor components. The evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

The instant claims encompass an isolated DNA molecule comprising any DNA sequence encoding at least 400 amino acids of a JAK3 kinase peptide of SEQ ID NO: 16, wherein said peptide has JAK kinase activity and undergoes tyrosine phosphorylation by at least one cytokine selected from the recited group or an isolated DNA molecule comprising any 1500 base nucleotide DNA sequence encoding an amino acid sequence of SEQ ID NO: 16, wherein the encoded amino acid sequence has the same activity or an isolated DNA molecule of claim 43 or claim 48, wherein said molecule comprises a DNA sequence encoding at least 400 amino acids of a JAK3 peptide of SEQ ID NO:16, wherein said peptide binds a receptor for a cytokine selected from the selected group of cytokines. However, the specification fails to teach

specifically which JAK3 kinase peptides derived from which encoded regions of the full-length JAK3 kinase of SEQ ID NO: 16 and which critical regions or domains of the JAK3 kinase that a JAK3 kinase peptide needs to possess in order have JAK kinase activity and undergoes tyrosine phosphorylation by one of the recited cytokines or binds a receptor for a selected group of cytokines. The instant specification merely demonstrates that full length JAK3 kinase is tyrosine phosphorylated and activated in response to various interleukins, G-CSF and GM-CSF in selected cells, as well as the tyrosine phosphorylation, activation and association with erythropoietin receptors and CNTF β receptor components for full length JAK1 and JAK2 kinases under certain conditions. In order for a JAK3 kinase peptide or any JAK kinase peptide to be activated or undergoing tyrosine phosphorylation or having cytokine receptor binding by one of the recited cytokines, one of skilled in the art needs to know exactly which domains or regions of the JAK3 kinase molecule are responsible for binding to any receptor of the recited group of cytokines, so that the recruited JAK3 kinase molecule or peptide can be activated or undergoing tyrosine phosphorylation. At the effective filing date of the present application, apart from the functional tyrosine kinase domain (JH1) at the carboxyl terminus of the JAK3 kinase molecule, the exact functions of conserved blocks of sequences (JH3-JH7) comprising approximately 600 N-terminal amino acid residues and the pseudokinase domain are not clearly determined, even in year 2000 (Rane & Reddy, Oncology 19:5662-5679, 2000; see page 5663, col. 2, bottom of second paragraph). Rane & Reddy also stated that the sequences of the JH3-JH7 domains bear no resemblance to any characterized protein motif. Additionally, the

three-dimensional structure for any JAK kinase, including JAK3 kinase, has not yet been elucidated. Furthermore, it is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties, let alone any extensive deletion or fragmentation or substitution or insertion. The present disclosure offers no guidance as to which regions or domains of the JAK3 molecule would be tolerant of alteration or fragmentation and which would not, which "particular" amino acid changes at which positions and in which combinations, such that a JAK3 kinase peptide having at least 400 amino acids of SEQ ID NO:16 or an amino acid sequence of SEQ ID NO:16 encoded by a 1500 base nucleotide DNA sequence can possess the desired properties of having JAK kinase activity and undergoing tyrosine phosphorylation by one of the recited cytokines. There is a high degree of unpredictability associated with the make and use of the claimed embodiment. In discussing peptide hormones, Rudinger has stated that "The significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstaking experimental study (Page 6, first sentence of Conclusions *In* J.A. Parsons, ed. "Peptide hormones", University Park Press, 1976). This unpredictability is further underscored by the fact that the relationship between the sequence of a peptide and its tertiary structure (or its activity) is not well understood and is not predictable (Ngo et al., *In* K. Merz et al., ed. "The protein folding problem and tertiary structure prediction", Birkhauser, 1994, 491-495). Moreover, the physiological

art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of guidance provided by the instant specification regarding to the issues set forth above, the unpredictability of the art on the protein/peptide folding and tertiary structure prediction, the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on February 26, 2002 in Paper No. 11 (pages 9-11) have been fully considered.

Applicants reiterated the argument that due to the fact that the amended claim 35 now reciting at least 400 amino acid limitation, such a fragment represents a significant portion of the complete sequence and one of skill in the art should have no difficulty in selecting the appropriate portion of the molecule to use the claimed invention. Examiner respectfully finds Applicants' argument to be unpersuasive for the following reasons.

Firstly, which 400 amino acid residues out of 1099 amino acid residues that the desired JAK3 kinase fragment contains? Which 699 amino acid residues in which regions or domains of the full-length JAK3 kinase should be deleted or substituted, such that JAK3 kinase fragment can still retain JAK kinase activity and interacts with any receptor of the recited group of cytokines so that said kinase fragment can undergo tyrosine phosphorylation or activated. As already noted above, at the effective filing date of the present application, apart from the functional tyrosine kinase domain (JH1) at the carboxyl terminus of the JAK3 kinase molecule, the exact functions of conserved blocks of sequences (JH3-JH7) comprising approximately 600 N-terminal amino acid residues and the pseudokinase domain are not clearly determined, even in the year 2000 (Rane & Reddy, Oncology 19:5662-5679, 2000; see page 5663, col. 2, bottom of second paragraph). The sequences of the JH3-JH7 domains bear no resemblance to any characterized protein motif and the three-dimensional structure for any JAK kinase, including JAK3 kinase, has not yet been elucidated. Furthermore, the significance of particular amino acids and sequences for different aspects of biological activity can not be predicted a priori or well understood as evidenced by the teachings of Rudinger and Ngo et al. With the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled in the art to make and use the instant broadly claimed invention.

Secondly, it is Applicants' opinion that one of skill in the art should have no difficulty in selecting the appropriate portion of the molecule to use the claimed invention. Unfortunately this is not considered to be a factual evidence indicating that

the unpredictability of the art on the protein/peptide folding and tertiary structure prediction can be overcome, such that one of skilled in the art could make and use the full breadth of the instant claimed invention without undue experimentation.

Applicants also argue "information such as critical kinase regions or domains of a protein with kinase activity are well known in the art and were used in developing the present invention. Furthermore, fig. 6 of the specification provides an amino acid sequence alignment between murine JAK 1, 2, and 3 and human Tyk2. Positions in the proteins in which three or more amino acids are identical are noted. The skilled artisan would recognize that conserved regions between two or more proteins having similar biological activity are indicative of regions important to biological activity. Here again, the skilled artisan would know to minimize or avoid making insertion, substitutions, or deletions of amino acid residues within these regions when attempting to produce a variant protein which retains JAK3 kinase and/or receptor binding activity which is at least 400 amino acids of SEQ ID NO: 16". Applicants' arguments are again respectfully found unpersuasive for the same reasons set forth in the immediate paragraphs above particularly in light of the teachings of Rane & Reddy, Ngo et al. and Rudinger.

Accordingly, claims 35, 36, 38, 45-46, 48 and amended 43 are rejected for the reasons stated above.

Double Patenting

Claims 42 and 51 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S.

Patent No. 6,136,595. Although the conflicting claims are not identical, they are not patentably distinct from each other. This is because the instant claims encompass the embodiment of claims 1-6 in the issued U.S. Patent No. 6,136,595. For example, an isolated DNA molecule that hybridizes to a DNA sequence encoding amino acid SEQ ID NO:16 under specified hybridization conditions, and wherein said isolated DNA molecule encodes a polypeptide having Jak kinase activity (**not** a Jak kinase peptide which is defined as any subset of a Jak kinase having JK activity by the instant specification, page 20 lines 4-6) and a tyrosine that is phosphorylated following IL-2 or IL-4 stimulation in claim 42 of the presently claimed invention would encompass an isolated DNA molecule comprising a DNA sequence encoding the JAK 3 kinase amino acid sequence of SEQ ID NO:16 or a JAK 3 kinase that is at least 80% or at least 80-99% or at least 95% homologous to the amino acid sequence of SEQ ID NO:16 of the claims in the issued U.S. Patent. In the issued U.S. patent, IL-2 and IL-4 have been shown to induce tyrosine phosphorylation of JAK 3 kinase (see col. 66 lines 1-32 of the issued patent). Similarly, an isolated DNA molecule wherein said molecule encodes a JAK3 kinase polypeptide (**not** a Jak kinase peptide which is defined as any subset of a Jak kinase having JK activity) that is at least 80-99% homologous to the amino acid sequence of SEQ ID NO:16, wherein the percent homology is determined using a GAP computer program having the recited default parameters in claim 51 of the present application would encompass an isolated DNA molecule encoding a JAK 3 kinase that is at least 80%-99% homologous to the amino acid sequence of SEQ ID NO: 16 in the issued U.S. Patent.

Responses to Arguments

Applicants' arguments related to the above rejection in the Supplemental Reply filed on June 20, 2002 in Paper No. 14 (pages 1-2) have been fully considered.

Applicants simply argue that the claims of the current application are not obvious in view of the claims of U.S. patent NO. 6,136,595. Applicants' argument is respectfully found unpersuasive for the reasons that are more clearly stated and elaborated above.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER